

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number  
**WO 2004/026294 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/195**,  
A61P 35/00, A23L 1/29

(CH). **WOLFE, Robert, R.** [US/US]; 4204 Pebble Beach  
Drive, League City, TX 77573 (US).

(21) International Application Number:  
PCT/EP2003/010482

(74) Agent: **BOHMANN, Christine**; Novartis AG, Corporate  
Intellectual Property, CH-4002 Basel (CH).

(22) International Filing Date:  
19 September 2003 (19.09.2003)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,  
GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ,  
OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ,  
TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/412,370 20 September 2002 (20.09.2002) US  
60/417,203 9 October 2002 (09.10.2002) US  
60/455,921 19 March 2003 (19.03.2003) US

(84) Designated States (*regional*): Eurasian patent (AM, AZ,  
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,  
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,  
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

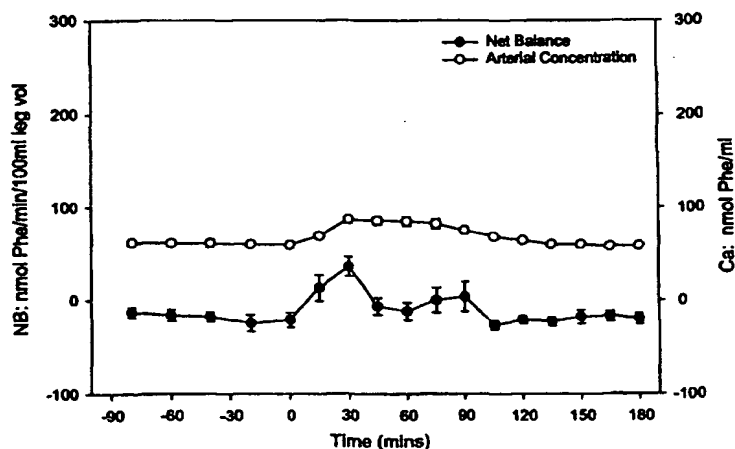
(71) Applicant (for all designated States except US): **NOVAR-  
TIS NUTRITION AG** [CH/CH]; Monbijoustrasse 118,  
CH-3001 Bern (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **TROUP, John, P.**  
[US/CH]; 8A Chemin des Marais, CH-1291 Commugny

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: LEUCINE-ENRICHED NUTRITIONAL COMPOSITIONS



(57) Abstract: Methods and nutritional or  
pharmaceutical compositions for promotion  
of muscle protein synthesis or controlling  
tumor-induced weight loss, such as cancer  
cachexia.

WO 2004/026294 A1

### Nutritional Compositions

Disclosed are methods and nutritional compositions for promotion of muscle protein synthesis or controlling tumor-induced weight loss, such as cancer cachexia.

- 5 Cachexia is a condition of severe malnutrition and negative nitrogen balance characterized by anorexia, i.e. a lack or severe loss of appetite, weight loss, and muscle atrophy. The physiological, metabolic, and behavioral changes in cachexia are associated with patient complaints of weakness, fatigue, gastrointestinal distress, sleep/wake disturbances, pain, listlessness, shortness of breath, lethargy, depression, malaise and the fear of being
- 10 burdensome on family and friends. Although cachexia has been classically associated with chronic infections and malignant conditions, it has also been identified in patients after extensive traumatic injury and sepsis, and in aging persons with failure to thrive syndrome. Loss of lean body mass associated with cancer cachexia not only weakens the individual and makes activities of daily living difficult, but can weaken the patient to the point that they
- 15 do not have the strength to undergo chemo-and/or radiation therapy.
- Two main components contribute to cancer cachexia – a loss of appetite, and a metabolic response to stress that causes a preferential loss of muscle at a rate greater than would be expected from the lack of nutritional intake alone. Consequently, a nutritional supplement to ameliorate the rate of loss of muscle mass in patients with cancer would have an important
- 20 clinical impact.

- Present inventors have found that when dietary intake is limited below the optimal level for physiological or pathophysiological reasons, a dietary supplement must be more effective than normal food intake to provide benefit. This is because in this circumstance, when a
- 25 dietary supplement is given, normal food intake is likely to be reduced by a calorically equivalent amount. Consequently, a supplement designed to limit cancer cachexia should stimulate muscle protein synthesis to a greater extent than normal food intake, and should not interfere with the response to meal intake.

- 30 Trials of conventional nutritional supplements in patients with cancer cachexia have failed to show appreciable benefit in terms of weight gain or quality of life. Accordingly, there is an urgent need for effective nutritional approaches capable of treating or preventing or

ameliorating the effects of tumor-induced weight loss, such as cancer cachexia and/or anorexia.

- 5 Present inventors have now found that a formulation containing free essential amino acids, rather than intact protein, is optimal. In particular, and unexpectedly, present inventors have found that nutritional compositions comprising a mixture of essential amino acids in free form and/or in salt form, rather than intact protein, which mixture comprises particularly high amounts of leucine effectively stimulate muscle protein synthesis.
- 10 Compositions of the invention, e.g. in the form of dietary means, e.g. supplements, or nutritional or pharmaceutical formulations, for the treatment or prevention of cachexia, e.g. cancer cachexia and/or anorexia can be self-administered for extensive periods without risk of adverse side-effects, yet have the potential to reverse cachexia, e.g. cancer cachexia, and/or improve associated symptoms that affect quality of life. The compositions as
- 15 described hereinafter have an excellent taste and thus have particularly good patient convenience and patient acceptance due to their increased ease of administration and ingestion.

- In one aspect of the present invention there is provided a composition comprising at least
- 20 one of isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, or histidine, e.g. leucine and at least one of isoleucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, or histidine, in free form and/or in salt form, e.g. pharmaceutically or nutritionally acceptable salt form, wherein leucine is present in an amount of at least about 10 to about 95%, e.g. about 10 to about 60%, e.g. at least about
- 25 15, 20, 25, 30 or 35% to about 40, 45, 50 or 55%, based on the weight of amino-nitrogen source, hereinafter referred to as compositions of the invention.

- The term "amino-nitrogen source" as used herein refers to amino acids, e.g. essential amino acids, conditionally essential amino acids or non-essential amino acids, in free form or salt
- 30 form, either alone or in combination with, e.g. in addition to, intact protein.

As used herein, the term "intact protein" refers to protein, e.g. hydrolyzed, e.g. partially hydrolyzed protein and to peptides, e.g. to amino acids which are not in free or salt form.

According to the invention, the "intact protein" may be chosen from at least one of casein, whey protein, soy protein, collagen or wheat protein.

5 In one aspect there is provided a composition of the invention, wherein leucine in free and/or salt form is present in amount of at least about 10 to about 35%, e.g. about 11, 12, 13, 14 or 15 to about 20, 25 or 30%, e.g. at least about 14 or 15% by weight, based on the weight of total amino acids.

10 In a further aspect of the invention there is provided a composition of the invention wherein leucine is present in free form and/or salt form in an amount of at least about 20 to about 80%, e.g. about 20 to about 65%, e.g. about 25, 30 or 35% to about 40, 45, 50 or 55%, e.g. about 65% by weight, based on the weight of amino acids in free form and/or salt form.

15 The term "amino acids" as used herein, unless otherwise stated, refers to amino acids in free form and/or in salt form chosen from at least one of essential amino acids, e.g. isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, or histidine, conditionally essential amino acids, e.g. tyrosine, cysteine, arginine, or glutamine, or non-essential amino acids, e.g. glycine, alanine, proline, serine, glutamic acid, aspartic acid, asparagines, taurine or carnitine.

20 In yet a further aspect there is provided a composition of the invention wherein leucine is present in free form and/or salt form in an amount of at least about 20 to about 95%, e.g. about 25, 30, 35, 40 or 45% to about 50, 55, 60, 65, 70, 75, 80, 85 or 90%, e.g. about 95% by weight, based on the weight of essential amino acids in free form and/or salt form.

25 The term "essential amino acids" (EAA) as used herein, unless otherwise stated, refers to essential amino acids in free form and/or salt form chosen from at least one of isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, and histidine. It is to be understood that "leucine" as used herein, unless otherwise stated, refers to leucine in  
30 free form and/or salt form.

The term "total leucine" or "total amino acid, e.g. essential or conditionally essential or non-essential amino acid" as used herein refers to leucine or amino acid in free and/or salt form plus leucine or amino acid derived from, or bound in, intact protein.

In a further aspect, there is provided a composition of the invention, wherein total leucine, i.e. the sum of leucine in free and/or salt form plus leucine derived from intact protein, is at least about 10 to about 40%, e.g. at least about 15 to about 35%, e.g. at least about 20 to about 30, e.g. about 21, 22, 23, 24 or 25%, e.g. about 22% by weight based on the weight of total amino acids. Total leucine content of the compositions of the invention may be from about 25 to about 45, e.g. about 30 to about 40%, e.g. about 36% of the total essential amino acids. The compositions of the invention may comprise leucine in free and/or salt form : leucine in form of intact protein in a ratio of about 3 : 1 to about 1 : 3, for example in a ratio of about 2 : about 1. In one aspect of the invention there is provided a composition of the invention comprising a ratio of total leucine : leucine in free and/or salt form of about 3 : 1 to about 1 : 3, e.g. about 1.5 : 1.

In yet a further aspect the present invention provides a composition of the invention, wherein the amount of leucine, e.g. total leucine, is up to three times higher than the highest amount of any other essential amino acid, e.g. total essential amino acid.

The invention also relates to compositions further comprising branched-chain amino acids, e.g. valine, leucine, isoleucine, or mixtures thereof, in free and/or in salt form and/or in form of intact protein, in an amount of about 30 to 60%, e.g. of about 35 to 55%, e.g. about 30 or 35 to 45% by weight based on the weight of amino-nitrogen source, e.g. of total amino acids.

In a further aspect of the invention there is provided a composition of the invention with a reduced amount of tryptophan or hydroxytryptophan in free and/or in salt form and/or in form of intact protein, e.g. about less than 5%, e.g. less than about 3% by weight based on the weight of amino-nitrogen source, e.g. of total amino acids.

The invention also relates to compositions of the invention further comprising threonine in free and/or in salt form and/or in form of intact protein in an amount of about 3 or 5 to about 11% by weight based on the weight of amino-nitrogen source, e.g. of total amino acids.

In a further aspect the invention relates to compositions of the invention further comprising valine in free and/or in salt form and/or in form of intact protein in amount of about 6% to

about 16%, e.g. about 8 to about 10% by weight based on the weight of amino-nitrogen source, e.g. based on the weight of total of amino acids.

5 In a further aspect of the invention the compositions of the invention may further comprise conditionally essential amino acids in free and/or in salt form and/or in form of intact protein chosen from at least one of arginine, glutamine, tyrosine, and cysteine.

10 In a preferred embodiment of the present invention, the compositions of the invention comprise arginine in free form and/or salt form, e.g. in an amount of about 5% or 10% to about 40%, e.g. about 15% to about 25%, 30% or 35%, e.g. about 15 to 20% by weight based on the weight of amino-nitrogen source, e.g. of the total essential and conditionally essential amino acids. In one aspect, free arginine constitutes about 5% to about 10%, e.g. about 7% of the total amino acids of the compositions of the invention.

15 In yet another embodiment of the invention the compositions, e.g. pharmaceutical or nutritional compositions, of the invention may have the following amino acid composition: leucine 20 to 35%, e.g. 30%, isoleucine 3 to 6%, e.g. 3 to 4%, valine 5 to 15%, e.g. 8 to 12%, methionine 0.5 to 7%, e.g. 2 to 5%, phenylalanine 8 to 12, e.g. 9 to 10%, lysine 10 to 14%, e.g. 12 to 13%, threonine 8 to 12%, e.g. 9 to 11%, histidine 8 to 12%, e.g. 8 to 11%,  
20 arginine 5 to 15% by weight based on the weight of amino-nitrogen source, e.g. of total amino acids. In a further aspect the compositions of the invention may comprise the following concentration range of amino acids (% molar base): leucine 20 to 40%, e.g. about 35 to 40%, isoleucine 3 to 10%, e.g. about 7%, valine 5 to 15%, e.g. about 10%, methionine 0.5 to 7%, e.g. about 5%, phenylalanine 5 to 12, e.g. about 5%, lysine 8 to 20%, e.g. about  
25 9%, threonine 6 to 12%, e.g. about 6%, histidine 3 to 8%, e.g. about 3%, tryptophan 0 to 4%, e.g. about 1%, arginine 5 to 15%, e.g. about 13%. The amino acids may be in free and/or in salt form and/or in form of intact protein, e.g. in free form, or predominantly in free form. In particular, the compositions of the invention may comprise arginine, leucine and methionine in free form and/or salt form, for example in the amounts of about 5% to about 15% arginine,  
30 about 10% to about 30% leucine, and about 0.5% to about 5% methionine by weight based on the weight of amino-nitrogen source, e.g. of total amino acids. In a further aspect the compositions of the invention may comprise arginine : leucine : methionine in free form and/or salt form in a ratio of about 0.1 to about 5 : about 0.5 to about 10 : about 0.01 to about 1, e.g. in a ratio of about 0.5 : about 1 : about 0.05.

In a further aspect of the present invention the compositions of the invention may further comprise glutamine, e.g. glutamine peptide, e.g. in an amount of about 4 to 9 g per daily dose.

5

In yet a further aspect of the present invention, the compositions of the invention further comprise intact protein, e.g. protein chosen from at least one of casein, whey protein, soy protein, collagen or wheat protein, preferably whey protein and/or soy protein and/or casein may be used. For example, the invention provides a composition comprising leucine in free  
10 form and/or in salt form and intact protein wherein leucine in free form and/or in salt form is present in an amount of about 10%, 15% or 20% to about 25%, 30% or 35%, e.g. about 15% to about 20%, e.g. about 18% by weight based on the weight of intact protein. The compositions of the invention may comprise intact protein : leucine in free and/or salt form in a ratio of about 10 : 1 to about 1 : 10, for example in a ratio of about 5 : 1 to about 1 : 5, for  
15 example in a ratio of about 5 : 1. The ratio of total amino acids : total leucine may be from about 3 : 1 to about 6 : 1, e.g. about 4 to 5 : 1.

In one aspect, present inventors have found that particularly high levels of essential and, optionally, conditionally essential amino acids may be provided using compositions  
20 comprising a combination of

- a) essential and, optionally, conditionally essential amino acids in free and/or salt form, and
- b) intact protein, wherein

the ratio of total essential and, optionally, conditionally essential amino acids to total amino  
25 acids is from about 0.4 to about 0.95, e.g. about 0.45, 0.5, 0.55 or 0.6 to about 0.7, 0.75, 0.8 or 0.9, e.g. about 0.65. In one aspect the compositions according to the invention provide a ratio of total essential and, optionally, conditionally essential amino acids versus total non-essential amino acids of about 0.65 : about 0.45. In a further aspect the compositions of the invention comprise about 40 to about 95%, e.g. about 45, 50, 55 or 60 % to about 70, 75, 80  
30 or 90%, e.g. about 65% by weight of total essential and, optionally, conditionally essential amino acids based on the weight of total amino acids.

In another specific embodiment of the present invention, the compositions of the present invention comprise a mixture of essential amino acids solely in free form and/or in salt form,

e.g. leucine solely in free form and/or in salt form and at least one essential amino acid solely in free form and/or in salt form.

5 According to the present invention, the compositions of the invention may be provided in form of dietary means, e.g. supplements, or in the form of a nutritional formulation, e.g. a medical food or beverage product, e.g. in form of a complete meal, part of a meal, as food additive or as powder for dissolution, or in the form of a pharmaceutical formulation, e.g. in form of a tablet, pill, sachet or capsule.

10 In a further aspect of the invention there is provided a medical food or beverage product, dietary supplement or nutritional or pharmaceutical formulation comprising a composition of the invention.

The compositions of the invention in form of dietary means, e.g. supplements, or  
15 pharmaceutical formulations may consist exclusively of the compositions of the invention, and optionally pharmaceutically or nutritionally acceptable carriers.

The compositions of the invention may be in medical food or beverage product form, e.g. in form of a powder for dissolution. The powder may be combined with a liquid, e.g. water, or  
20 other liquid, such as milk or fruit juice, e.g. in a ratio of powder to liquid of about 1 to about 5, to obtain a ready-to-consume composition, e.g. ready-to-drink composition or instant drink.

Optionally, the compositions according to the invention may be nutritionally complete, i.e. may include vitamins, minerals, trace elements as well as nitrogen, carbohydrate and fat  
25 and/or fatty acid sources so that they may be used as the sole source of nutrition supplying essentially all the required daily amounts of vitamins, minerals, carbohydrates, fat and/or fatty acids, proteins and the like. Accordingly, the compositions of the invention may be provided in the form of a nutritionally balanced complete meal, e.g. suited for oral or tube feeding, e.g. by means of nasogastric, nasoduodenal, esophagostomy, gastrostomy, or  
30 jejunostomy tubes, or peripheral or total parenteral nutrition. Preferably the compositions of the invention are for oral administration.

Surprisingly and unexpectedly, present inventors have found that particularly useful compositions for promotion of muscle protein synthesis or controlling tumor-induced weight



loss, such as cachexia, e.g. cancer cachexia, may be obtained by combining the mixture of essential amino acids in free form and/or in salt form, alone or in combination with intact protein, as hereinabove described with n-3 polyunsaturated fatty acids, including, but not limited to alpha-linolenic acid (LNA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), either alone or in combination with each other. The effect of such a combination is greater than the effect that can be achieved with either type of combination partner alone, i.e. greater than the effect of a nutritional therapy using only the mixture of essential amino acids in free form and/or in salt, alone or in combination with intact protein, or the n-3 fatty acid(s) as defined herein.

10

Hence, in one aspect the present invention further pertains to a combination comprising

- (a) a mixture of essential amino acids in free and/or in salt form, wherein leucine, e.g. total leucine, is at least about 10 to about 40%, e.g. at least about 15 to about 35%, e.g. at least about 20 to about 30, e.g. about 15% to about 25%, e.g. about 22%, by weight based on the weight of amino-nitrogen source, e.g. of total amino acids, and
- (b) at least one n-3 fatty acid chosen from alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid,

15

wherein leucine may be present in form of a combination of leucine in free and/or salt form and leucine derived from intact protein and the n-3 fatty acid(s) may be present in free form or in form of an oil or fat, e.g. for promotion of muscle protein synthesis or controlling tumor-induced weight loss, such as cachexia, e.g. cancer cachexia.

20

Such a combination is preferably a combined preparation or a pharmaceutical or nutritional composition.

25

Preferably the compositions of the invention may comprise EPA and DHA, e.g. EPA and DHA in a ratio of EPA : DHA of about 2 : 1 to about 1 : 2, e.g. about 1.5 : 1.

30

In a further aspect of the invention the compositions of the invention may comprise EPA and DHA either alone or in combination, e.g. EPA alone, in an amount of at least about 600 mg to about 2 g, e.g. about 1.5g to about 1.8g per serving. When combined, EPA may be present in amount of about 500 mg to about 1.5 g, e.g. about 1g, and DHA may be present in an amount of about 250 mg to about 1.5 g, e.g. about 500 mg to about 750 mg, e.g. about 650 mg, per serving.

In yet a further aspect of the invention the compositions of the invention may comprise a mixture of n-6, e.g. linoleic acid, and n-3 polyunsaturated fatty acids, e.g. chosen from linolenic acid, EPA and DHA, e.g. in a ratio of n-6 : n-3 polyunsaturated fatty acids of about 0.1 : 1 to about 1 : 0.1, e.g. about 0.2, 0.5 or 0.8 to about 1, 1.2 or 1.5, e.g. about 1.1 : 1.

5

In a further aspect the compositions of the invention may comprise about 2g or 2.5 to about 3.5g, e.g. about 2.5g or 3g per serving of monounsaturated fatty acids (MUFA) and about 3g or 3.5g to about 4g or 6g, e.g. about 4.5g or 5g per serving of polyunsaturated fatty acids (PUFA).

10

Nutritional formulations comprising the compositions of the invention, e.g. medical food or beverage product, comprise other nutritional components, e.g. fats and/or carbohydrates, in addition to the mixture of essential amino acids in free and/or in salt form and optionally the n-3 fatty acid(s). Dietary oils may be used in the preparation of the nutritional compositions of the invention. Dietary oils include but are not limited to canola, medium chain triglycerides (MCT), fish, soybean, soy lecithin, corn, safflower, sunflower, high-oleic sunflower, high-oleic safflower, olive, borage, black currant, evening primrose and flaxseed oil. Preferably fish oil may be used, e.g. an oil comprising about 45% EPA and about 10% DHA, e.g. as known and commercially available under the trade name EPAX® 4510 from Pronova Biocare, Norway, or concentrated fish oil, comprising e.g. about 70% EPA.

20

The dose of dietary oil per serving, e.g. in the form of fish oil, may comprise for example about 0.5 g to about 3 g, e.g. about 1.5 g to about 2 g, of n-3 polyunsaturated fatty acids.

25

The dose of dietary oil per serving may comprise for example about 2.5 g, 3.5 g or 4.5 g to about 5.5 g, 6.5 g or 7.5 g, e.g. about 5.5 g of fish oil and/or about 0.5 g, 1 g, 1.5 g, 2 g or 2.5 g to about 3 g, 3.5 g, 4 g, 4.5 g or 5 g, e.g. about 1 g to about 3 g, e.g. about 1g of medium chain triglycerides (MCT).

30

According to the invention, up to 5 or 6, e.g. about 2 to 3 servings may be given per day.

In a further aspect of the present invention the compositions of the invention, e.g. nutritional compositions, may further comprise soluble fibers, e.g. agar, alginates, carubin, pectin and its derivatives, e.g. pectins from fruits and vegetables, and more preferably pectins from

citrus fruits and apple, beta-glucan, such as oat beta-glucan, carrageenans, e.g. kappa, lambda and iota carrageenans, furcellaran, inulin, arabinogalactan, cellulose and its derivatives, scleroglucan, psyllium, such as psyllium seed husk, mucilages and gums.

According to the invention, gums and mucilages are preferably plant exudates. In particular,  
5 the term "gum" as used herein refers to the commonly available vegetable gums and more particularly to konjac gum, xanthan gum, guar gum (guaran gum), locust bean gum, tara bean gum, gum tragacanth, arabic gum, karaya gum, gum ghatti, gellan gum and other related sterculia gum, Alfalfa, Clover, Fenugreek, Tamarind flour. Native and modified, e.g. hydrolyzed, soluble fibers may be used according to the invention. According to the  
10 invention, preferably guar gum, e.g. hydrolyzed guar gum, may be used.

The compositions of the invention may further deliver about 5 g to about 15 g per day, e.g. about 9 g per day soluble fiber, for example in the form of inulin and hydrolyzed guar gum, e.g. in 3 servings of about 3 g.

15

In one embodiment of the present invention the daily delivery of amino-nitrogen source may be from about at least 10 g to about 60g, e.g. from about 15 g to about 55 g, e.g. about 20 to about 50 g, e.g. about 44 to about 54 g. Optimally at least about 6 g to about 18 g, e.g. about 10 g to about 12 g of the total amino-nitrogen source per daily dose are amino acids in  
20 free form and/or in salt form. At least about 3 g up to about 15 g, e.g. about 6 g, 7.5 g, 8 g or 8.5 g to about 12 g, e.g. about 8 g of the total amino-nitrogen source per daily dose are essential amino acids in free form and/or in salt form. The daily dose of e.g. about 15 g essential amino acids, e.g. in free and/or salt form, may be given 3 times per day, e.g. in 3 servings of about 5 g, with equal effectiveness. In one aspect the daily delivery of leucine in  
25 free and/or salt form may be from about 5 g to about 10 g, e.g. in an amount of about 8 g. The daily delivery of total leucine may be from about 10 g to about 20 g, e.g. about 12 g to about 15 g, e.g. about 12 g. In one aspect of the invention total essential and, optionally, conditionally essential amino acids may be delivered in an amount of from about 6 to about 21 g per serving, e.g. from about 6 to about 12 g per serving.

30

The daily delivery of the optional nutrients referred to hereinabove may vary depending on body weight, sex, age and/or medical condition of the individual. All indicated proportions described above are accordingly to be understood as being indicative of preferred or individually inventive teaching only and not limiting the invention in its broadest aspect.

In a further embodiment of the invention, the nutritional product provides at least 100%, e.g. 100%, of the U.S. RDA for vitamins and minerals per daily dose.

- 5 The present inventors have found that particularly high amounts of vitamin E are useful in the compositions as hereinabove described for promotion of muscle protein synthesis or controlling tumor-induced weight loss, such as cachexia, e.g. cancer cachexia.

- 10 Hence, in a further aspect the invention also pertains to compositions of the invention further comprising tocopherol and/or tocotrienol, e.g. Vitamin E (alpha-tocopherol), in an amount of about 50 mg to about 400 mg, e.g. about 100 mg or 200 mg to about 300, e.g. about 150, 240 mg or 300 mg per daily dose, e.g. in 3 servings of about 50 or 100mg.

- 15 The caloric density of the compositions, e.g. nutritional compositions of the invention may be about 1.5 kcal/mL, e.g. about 600 to about 1500 kcal per day, e.g. about 720 to about 900 kcal per day, in the form of about 2 to about 5 or 6 servings per day, e.g. in 3 servings of about 310 kcal. A suitable serving size may be in the range of about 20 to about 500 ml, preferably about 50 to about 250ml, e.g. about 200 or 240 ml. The compositions of the invention may provide benefit with as few as for example two servings per day. Levels of
- 20 amino-nitrogen source, e.g. intact protein or amino acids, e.g. essential amino acids, or fatty acids, or carbohydrate on a per liter basis are not crucial, provided that a reasonable volume supplies the recommended amounts in accordance with the invention. A typical nutritional composition useful according to the invention will have a caloric distribution of about 12 to about 24%, e.g. about 23% from a source of amino nitrogen, e.g. protein, e.g. amino acids in
- 25 free form and/or in salt form in combination with intact protein, about 40 to about 65%, e.g. about 46% from carbohydrate, for example in the form of maltodextrin and sucrose, and about 10 to about 35%, e.g. about 30% from fat, for example in the form of fish and vegetable oil.

- 30 Nutritional compositions in accordance with the present invention may be provided as a medical food or beverage product, e.g. in oral nutritional form, e.g. as a health drink, as a ready-made drink, optionally as a soft drink, including juices, milk-shake, yoghurt drink, smoothie or soy-based drink, in a bar, or dispersed in foods of any sort, such as baked

products, cereal bars, dairy bars, snack-foods, soups, breakfast cereals, müesli, candies, tabs, cookies, biscuits, crackers (such as a rice crackers), and dairy products.

- Preferably the compositions of the invention may be administered as a nutritional  
5 formulation, e.g. as part of a meal, e.g. in the form of a health drink, e.g. ready-to-use drink.

- Nutritional compositions in accordance with the present invention may be administered in form of a single composition that contains all components, e.g. essential amino acids, fatty acids and/or soluble fibers, or each component may be administered individually. For  
10 example a liquid nutritional formulation, e.g. in the form of a syrup, suspension, emulsion or solution, may contain all components except for the essential amino acids, e.g. except for the branched-chain amino acids and/or glutamine, e.g. glutamine peptide, if present. For example, the branched-chain amino acids and/or glutamine, e.g. glutamine peptide, if present, may be administered in form of a solid oral dosage form, e.g. in form of a capsule,  
15 pill, tablet, dragées, or sachet.

Solid oral dosage forms are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes.

- 20 For example, compositions for oral administration may be obtained by combining the active ingredients with solid carriers, optionally granulating a resulting mixture and processing the mixture or granules, if desired or necessary after the addition of suitable excipients, to form tablets or dragée cores.
- 25 Suitable physiologically acceptable carriers may be especially fillers, such as sugars, for example lactose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, such as the  
30 above-mentioned starches, and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. In one aspect of the invention the compositions of the invention may be lactose-free. Further excipients may be especially flow-conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are

provided with suitable coatings, there being used *inter alia* concentrated sugar solutions which may contain gum Arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable compositions may be in the form of hard gelatin capsules or soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the composition of the invention in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, if desired, stabilisers. In soft capsules the composition of the invention is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it is likewise being possible to add stabilisers.

Conventional additives may be included in the compositions of the invention, including any of those selected from preservatives, chelating agents, osmotic agents, buffers or agents for pH adjustment, effervescing agents, sweeteners, e.g. artificial sweeteners, flavoring agents, coloring agents, taste masking agents, acidulants, emulsifiers, stabilizers, thickening agents, suspending agents, dispersing or wetting agents, antioxidants, acidulants, texturisers, antifoams, and the like.

In addition to the foregoing the present invention also provides a process for the production of a composition, e.g. nutritional or pharmaceutical formulation, as hereinbefore defined, which process comprises bringing the individual components thereof into intimate admixture and, when required compounding the obtained composition in a food or beverage product, for example ready-made drink, or in unit dosage form, for example filling said composition into gelatin capsules.

In another aspect the present invention provides a method for controlling tumor-induced weight loss, such as cachexia, e.g. cancer cachexia, e.g. treating or preventing or ameliorating the effects of cachexia, e.g. cancer cachexia, and/or anorexia, comprising enterally administering to a human in need of such treatment any composition disclosed herein.

In yet a further aspect the present invention provides for promotion of or stimulating muscle protein synthesis, or ameliorating loss of muscle in a human comprising enterally administering to a human in need of such treatment a composition of the invention.

5

In yet a further aspect the invention provides a method of preventing catabolism and increasing protein synthesis in a subject undergoing metabolic stress, which comprises administering to a human in need of such treatment a composition of the invention.

- 10 The invention further provides a use of the compositions as described herein for the dietary management of malnutrition, e.g. protein-energy malnutrition.

- 15 In yet another aspect of the invention there is provided a use of the compositions of the invention in the manufacture of a medicament for the treatment and/or prevention of tumor-induced weight loss, such as cachexia, e.g. cancer cachexia, and/or anorexia, ameliorating the effects of cachexia, e.g. cancer cachexia, and/or anorexia, stimulating muscle protein synthesis, or ameliorating loss of muscle in a human.

- 20 The method of treatment or use as claimed herein is applicable to tumor-induced weight loss, such as cancer cachexia, or anorexia in human patients suffering from different cancers, e.g. liver, breast, lung, prostate, gastrointestinal or pancreatic cancer. Cachexia or anorexia may be related to the disease itself or the effects of treatment.

- 25 The method of treatment or use according to the invention may be combined with pharmacological and alternative/complementary medicine therapies and/or with educational interventions, e.g. to treat and manage the physical and emotional symptoms associated with cachexia, e.g. cancer cachexia, and/or anorexia. For example, the compositions of the invention may be combined with anti-cancer drugs, such as 5-fluorouracil, mitomycin-C, adriamycin, chloroethyl nitrosureas and methotrexate. In a further aspect the compositions  
30 may be combined with interleukin-15.

In a further aspect of the present invention there may be provided a combined pharmaceutical formulation for simultaneous, separate or sequential use for the treatment or

prevention of cachexia, e.g. cancer cachexia, and/or anorexia comprising a composition of the invention, and one or more anti-cancer drug(s).

5 Dependent on the form of application of the compositions of the invention, i.e. as complete meal, part of a meal, food additive, drink, sachet, tablet or capsule, the compositions of the invention may be taken once daily to five or six times daily. For patients using the compositions of the invention as a supplement to a normal diet, the daily dose may be 2 servings per day. For patients receiving the compositions of the invention as their entire daily nutritional intake, up to six servings per day may be recommended. The compositions of the  
10 invention may be served without restriction to time of day, e.g. together with the main meals, preferably between meals.

The compositions of the invention may be administered under the supervision of a medical specialist, or may be self-administered.

15

For treatment of tumor-induced weight loss, such as cachexia, e.g. cancer cachexia, and/or anorexia under clinical supervision it is possible to combine the nutritional approach with conventional pharmaceutical therapies such as anti-cancer drugs. The anti-cancer drugs may conveniently be formulated together with the compositions of the invention in standard  
20 pharmaceutical dosage forms. In a further aspect of the invention the composition of the invention may be provided in form of a kit for separate, sequential or simultaneous administration in conjunction with one or more anti-cancer drug(s).

25 Optimally, the composition, e.g. nutritional composition or dietary supplement, of the invention is consumed for the duration of patient care and treatment, e.g. until weight is regained or lean body mass is increased. Since these formulations are safe to consume, cachectic or anorectic patients, can continue taking these supplements for as long as required, e.g. until normal weight or lean body mass has been resumed. Early intervention may be a critical success factor for improved outcome in patients with cachexia, e.g. cancer  
30 cachexia.

Anyone perceived to be at risk from tumor-induced weight loss, e.g. cachexia and/or anorexia or subjects already suffering from cachexia, e.g. cancer cachexia, and/or anorexia, can benefit from ingesting the compositions of the invention. The compositions of the



invention may be particularly indicated for patients with solid tumours with cachexia or at risk of developing it. By stimulating muscle protein anabolism, the compositions of the invention have the potential to reduce the rate of or reverse tumor-induced weight loss, e.g. cachexia, to promote weight gain, stimulate muscle growth, to enhance immune function, to restore  
5 metabolic balance, to support increased resistance to infection, improved tolerance to cancer therapy, enhanced response to cancer therapy, to reduce morbidity, to improve associated symptoms that affect quality of life, such as weakness, fatigue, gastrointestinal distress, sleep/wake disturbances, pain, listlessness, shortness of breath, lethargy, depression, malaise.

10

In accordance with the invention as presently claimed it is possible to effectively ameliorate symptoms and conditions associated with tumor-induced weight loss, e.g. cachexia and/or anorexia with natural compounds, which do not show any severe side effects. Further, the present methods are well-tolerated, for example without causing any discomfort or nausea,  
15 and simple to apply.

15

The utility of all the compositions of the present invention may be observed in standard clinical tests in, for example, indications as described hereinabove, for example using dosages of amino acids in free form and/or in salt form, in the range of about 0.05 to about  
20 0.3 g/kg body weight/day, preferably from about 0.085 to about 0.25 g/kg body weight/day, more preferably from about 0.1 or 0.15 to about 0.2 g/kg body weight/day, or using dosages of total essential amino acids in the range of from about 6 to about 12g or up to about 21 g per serving, or from about 36 to about 72 g total essential amino acids per day, for a mammal, e.g. adult, and in standard animal models. The effect of the compositions of the  
25 invention, on prevention and treatment of tumor-induced weight loss, e.g. cachexia can be monitored by any of the methods known to one skilled in the art, e.g. food intake, body weight, anthropometric measurements, serum levels of lipids, fatty acids, amino acids, levels of serologic markers, serotonin, C-reactive protein, TNF alpha, IL-1, changes in the morphology of tumors.

25

30

One human clinical trial may be affected as follows:

A randomised double blind study comparing the compositions of the invention, e.g. using dosages of amino acids in free form and/or in salt form, in the range of about 0.05 to about 0.3 g/kg body weight/day, preferably from about 0.085 to about 0.25 g/kg body weight/day,

more preferably from about 0.1 or 0.15 to about 0.2 g/kg body weight/day and dosages of n-3 polyunsaturated fatty acids in the range of about 0.05 to about 0.3 g/kg body weight/day, preferably from about 0.06 to about 0.2 g/kg body weight/day, more preferably from about 0.06 to about 0.13 or 0.15 g/kg body weight/day, or using dosages of total essential amino acids in the range of from about 6 to about 12g or up to about 21 g per serving, or from about 36 to about 72 g total essential amino acids per day, to a standard nutritional supplement may be performed in patients with advanced pancreatic cancer aiming at comparison of the effect on lean body mass, assessment of the effect on mediators in serum and urine, pro-inflammatory cytokines and muscle metabolism, and assessment of changes in performance status, quality of life and survival. 125 patients per treatment group may be tested, e.g. assessing the following parameters: change in lean body mass between baseline and week 12, body weight, nutritional intake and fatty acid analysis. In addition, for a subgroup of 40 patients, baseline versus 3 weeks investigations may be undertaken for: Urinary Proteolysis Inducing Factor, acute phase protein response (C-reactive protein concentration) and pro-inflammatory cytokines, Ubiquitin metabolism (muscle biopsy in 15 patients) and the acceptability of the product, e.g. taste, and compliance with the treatment regimen.

The invention will now be further illustrated by the following examples.

20

#### Example 1

An experiment was performed in healthy older subjects ( $\bar{x}=71\pm 2$  yr) to determine if non-essential amino acids, i.e. amino acids synthesized within the body at a rate sufficient to provide daily requirements, are needed for an amino acid mixture to stimulate muscle protein synthesis. The response of muscle protein metabolism to either 18 g of essential amino acids (EAAs) or 40 g of balanced amino acids (BAA, EAAs + 22g non-essential amino acids) given orally over a 3h period was compared. Muscle protein metabolism was measured in the basal state and during oral amino acids using L-<sup>2</sup>H<sub>5</sub>-phenylalanine infusion, femoral arterial and venous catheterization, and muscle biopsies. The exact mixtures of amino acids tested are shown in Table 1.

30

**Table 1.** Amino acids content of the two supplements administered to the two groups of older subjects.

The supplements were made of crystalline amino acids and dissolved in 540 ml of water containing a sugar-free flavor.

	Essential Amino Acids	Balanced Amino Acids
Alanine (g)	-	2.4
Arginine (g)	-	2.8
Asparagine (g)	-	3.7
Cysteine (g)	-	0.5
Glutamine (g)	-	5.8
Glycine (g)	-	1.8
Histidine (g)	2.0	2.0
Isoleucine (g)	1.9	1.9
Leucine (g)	3.2	3.2
Lysine (g)	3.9	3.9
Methionine (g)	1.0	1.0
Phenylalanine (g)	1.6	1.6
Proline (g)	-	1.9
Serine (g)	-	1.6
Threonine (g)	1.9	1.9
Tryptophane (g)	0.5	0.5
Tyrosine (g)	-	1.4
Valine (g)	2.2	2.2
<b>Total Amino Acids (g)</b>	<b>18.2</b>	<b>40.1</b>
<b>Total Energy (kJ [kcal])</b>	<b>309 [74]</b>	<b>682 [163]</b>

5

**Results** Net muscle protein synthesis (reflected by phenylalanine kinetics) increased similarly from basal ( $p < 0.01$ ) in both groups (BAA:  $-16 \pm 5$  to  $16 \pm 4$ ); EAA:  $-18 \pm 5$  to  $14 \pm 13$   $\text{nmol} \cdot \text{min}^{-1} \cdot 100 \text{ ml leg}^{-1}$ ) due to a similar increase ( $p < 0.01$ ) in muscle protein synthesis (BAA:  $43 \pm 10$  to  $67 \pm 11$ ; EAA:  $62 \pm 6$  to  $75 \pm 10$   $\text{nmol} \cdot \text{min}^{-1} \cdot 100 \text{ ml leg}^{-1}$ ) and no change in breakdown.

10 The results indicate that essential amino acids are solely responsible for the amino acid-induced stimulation of muscle protein anabolism.

### Example 2

The effect of a mixture of free essential amino acids on muscle protein synthesis stimulation was compared with the effect of a same amount of protein. Elderly volunteers ( $n=5$ ) were given 15 g of free essential amino acids (leucine, isoleucine, methionine, phenylalanine, histidine, lysine, and threonine) on one occasion and 15 g of whey protein on another. The results are shown in Figures 1 and 2. Net muscle protein synthesis, i.e. the balance between protein synthesis and breakdown, was measured using the A-V balance technique and stable isotope tracers, as described in Biolo et al, Am J Physiol 267(39):E467-474, 1994,

15

20

which is hereby incorporated by reference. Even though whey protein is a rapidly absorbed protein, as compared to other proteins such as casein, the change in plasma phenylalanine concentration (representative of all EAAs) was modest and transient (Figure 1). In contrast, phenylalanine concentration peaked rapidly and at a much higher concentration after  
5 ingestion of the free EAAs (Figure 2). The response of net protein synthesis is also shown in Figures 1 and 2. The pattern of net balance corresponded to the changes in concentration. The total response to the EAA drink was more than twice that of the intact protein, even though comparable amounts of N were ingested (Figure 3).  
10 The results indicate that ingestion of EAAs is more effective than ingestion of a comparable amount of intact protein in stimulating net muscle protein synthesis in unstressed elderly individuals.

**Figure 1** shows response of plasma phenylalanine concentration and net balance (reflection of net protein synthesis) to ingestion of 15g of whey protein.

15

**Figure 2** shows phenylalanine concentration and net balance in response to 15g of a solution of essential amino acids (EAAs).

**Figure 3** shows comparison of total response of net muscle protein synthesis to EAAs vs whey protein. Significantly different,  $p < 0.001$ .

20

### Example 3

To investigate the optimal mixture of free amino acids for stimulating net muscle protein  
25 synthesis a series of studies in New Zealand white rabbits weighing about 4.5 kg was performed. Net muscle protein balance was quantified by a technique analogous to the one used for human studies as described in Biolo et al, J Parent Enteral Nutr 16:305-315, 1992, which is hereby incorporated by reference, except that leg blood flow was measured by flow probe. This animal model is designed to represent a stress model induced by the surgical  
30 procedures needed to collect the samples and therefore is considered to be a good model for a seriously-ill cancer patient. Different amino acid mixtures were infused into the rabbits, and the response of muscle quantified.

The groups were as follows:

Controls: No amino acids

AA group: A balanced AA solution (10% Travasol®) containing all amino acids  
( $27.3 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )

EAA group: Only essential amino acids ( $27.3 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )

5 Leu (25%) + AA group: Leucine was added to the balanced AA solution to account for 25% of total nitrogen and infused at the same total nitrogen group as others  
( $27.3 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )

Leu (35%) + AA group: Same as above, except Leu comprised 35% of total

Leu only: Leucine only at  $8.3 \mu\text{mol}\cdot\text{kg}\cdot\text{min}$

10

The amino acid composition of each mixture is shown in Table 2.

15

**Table 2.** Amino acid composition in 100 ml of the infusion solutions.

		Balanced	EAA	Leu (25%)+AA	Leu (35%)+AA	Leu
20	Leu	730 mg	1.86 g	3.63 g	5.02 g	4.37 g
	Ile	600 mg	1.01 g	472 mg	390 mg	0
	LysHCl	580 mg	1.56 g	456 mg	377 mg	0
	Val	580 mg	1.15 g	456 mg	377 mg	0
	Phe	560 mg	1.56 g	441 mg	287 mg	0
25	His	480 mg	1.09 g	378 mg	312 mg	0
	Thr	420 mg	1.47 g	330 mg	273 mg	0
	Met	400 mg	0.31 g	315 mg	260 mg	0
	Trp	180 mg	0.11 g	142 mg	117 mg	0
	Ala	2.07 g		1.63 g	1.35 g	0
30	Arg	1.15 g		905 mg	748 mg	0
	Gly	1.03 g		810 mg	670 mg	0
	Pro	680 mg		535 mg	442 mg	0
	Ser	500 mg		393 mg	325 mg	0
	Tyr	40 mg		31 mg	26 mg	0
35						

Table 3 compares the amount of leucine infused as a function of total N.

**Table 3.**

(1) Leucine infusion

40

Solution	Leu infused $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	Total N infused $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	% of Leu to total N
Travasol®	1.39	27.3	5%

EAA	4.37	27.3	16%
Leu (25%)+AA	6.93	27.3	25%
Leu (35%)+AA	9.58	27.3	35%
Leu alone	8.75	8.75	100%

5

Data are means  $\pm$  SEM in  $\mu\text{mol/kg}^{-1}\text{min}^{-1}$ . \* $p < 0.05$  vs. control. In the EAA group no statistical analysis was done.

The results are shown in Table 4.

10 **Table 4. Protein kinetics in muscle**

	Synthesis	Breakdown	Net balance
Control (n=6)	$5.4 \pm 0.6$	$9.2 \pm 1.1$	$-3.8 \pm 0.5$
15 Travasol® (n=6)	$4.3 \pm 0.7$	$8.7 \pm 1.0$	$-4.4 \pm 1.0$
EAA (n=4)	$4.6 \pm 1.2$	$9.5 \pm 1.7$	$-4.9 \pm 0.6$
Leu (25%)+AA (n=6)	$6.8 \pm 1.1^*$	$8.1 \pm 1.2$	$-1.2 \pm 0.2^*$
Leu (35%)+AA (n=8)	$6.9 \pm 0.6^*$	$8.0 \pm 0.4$	$-1.0 \pm 0.4^*$
20 Leu alone (n = 5)	$6.6 \pm 0.7$	$9.2 \pm 0.5$	$-2.6 \pm 0.3$

Data are means  $\pm$  SEM in  $\mu\text{mol/kg}^{-1}\text{min}^{-1}$ . \* $p < 0.05$  vs. control.

Neither a balanced solution, nor the EAA solution, stimulated net muscle synthesis at the dosage given. In contrast, when the mixture was enriched with leucine a stimulatory effect on synthesis was observed.

25

#### Example 4

Mixtures of EAAs + arginine for nutritional supplement effective in ameliorating loss of muscle in cancer patients. Values are % of total amino acids (molar base).

	4.1	4.2	4.3	4.4
				Range
Leucine	30	30	38.8	25-40
Isoleucine	3	4	7.4	3-10
Valine	9	8	10.4	5-10
Methionine	3	5	4.6	1-5
Phenylalanine	10	9	5.5	5-12
Lysine	13	12	9.4	8-20
Threonine	9	11	6.4	6-12
Histidine	8	11	3.4	3-8
Arginine	15	10	13.0	10-15
Tryptophan	-	-	1.2	1-4
	100	100	100	62-115

**Example 5**

A cancer supplement in form of a ready to drink composition.

**Example 5A**

	<u>Percent</u>	<u>Grams/serv.</u>
Water	66.6667	176.667
Canola Oil	1.8567	4.920
MCT Oil	1.0411	2.759
EPAX® 4510 (Marine Oil)	1.1878	3.148
DHA Gold® (Algae Oil)	0.3511	0.930
Ca Caseinate	6.8900	18.259
Benefiber®	1.6978	4.499
Arginine	0.6944	1.840
Leucine	0.5511	1.460
Valine	0.2978	0.789
Methionine	0.0300	0.080
Phenylalanine	0.2456	0.651
Sucrose	7.6089	20.164
Corn Syrup (25DE)	9.4344	25.001
Potassium Citrate	0.1889	0.501
Sodium Citrate	0.1889	0.501
Lactic Acid	0.0444	0.118
Flavor	0.3989	1.057
Sucrolose	0.0700	0.186
Sodium Chloride	0.0400	0.106
Mono- and Diglycerides	0.1322	0.350
Antifoam	0.0022	0.006
Sodium Ascorbate	0.0300	0.080
Vit/Min Premix	0.3511	0.930
	100.000	265.000
Total (per 100g)		
Total (per serving)		265Grams

5

**Example 5B**

	<u>Grams per Serving</u>	<u>Formula Percent</u>
Water	173.95	65.6410
MCT Oil	1.2	0.4528
Canola Oil	0.6	0.2264
Sun Oil	4.5	1.6981
EPAX 3000TG	5.7	2.1509
Mixed Tocopherols	0.0024	0.0009
Ca Caseinate	18.26	6.8905
Benefiber	1.35	0.5094
F O S	2.3	0.8679
Arginine	1.49	0.5623
Leucine	3.13	1.1811

Methionine	0.18	0.0679
Sucrose	9	3.3962
25DE Corn Syrup	38	14.3395
Potassium Citrate	0.5	0.1887
Sodium Citrate	0.5	0.1887
Lactic Acid	1.25	0.4717
Flavor	0.8	0.3019
Flavor	0.4	0.1509
Sucrolose	0.132	0.0498
Salt	0.2	0.0755
Monos and Diglycerides	0.490	0.1849
Lecithin	0.133	0.0502
Antifoam	0.0045	0.0017
Sodium Ascorbate	0.08	0.0302
Vit/Min Premix	0.85	0.3208
	265.0019	100.000

Method: Water is heated to 160F and all ingredients except for EPAX® 4510, DHA Gold®, Flavor, Sucrolose, Sodium Chloride, Sodium Ascorbate and Lactic Acid are added. The mixture is cooled to less than 100F and the pH adjusted to 6.5 with Lactic Acid. The mixture is heated to 140F under agitation and after 5 min holding time homogenized at 2500 psi. Remaining ingredients are added and the mixture preheated to 150F, heated at 290F for 4 sec and homogenized at 2500 psi.

As Vitamin/Mineral Premix the following composition may be used:

10	MALTODEXTRIN POWDER 10 DE	37.404155
	DIPOTASSIUM PHOSPHATE	35.701500
	MAGNESIUM OXIDE	8.330400
	VITAMIN E ACETATE	7.168900
	TRICALCIUM PHOSPHATE	4.760200
15	FERROUS SULFATE	1.387600
	ZINC SULFATE	1.042500
	BIOTIN, 1% TRITURATION	0.933000
	NIACINAMIDE (B3)	0.761600
	VITAMIN A PALMITATE	0.606900
20	CALCIUM PANTOTHENATE	0.430800
	COPPER GLUCONATE	0.380800
	VITAMIN K	0.297500
	CYANOCOBALAMIN (B12)	0.202300
25	MINERAL, MANGANESE SULFATE, (MONOHYDRATE), USP, KOSHER	0.172860
	VITAMIN D3	0.119000
	PYRIDOXINE HYDROCHLORIDE (B6)	0.095200
	POTASSIUM IODIDE 10%	0.055258
	THIAMINE HYDROCHLORIDE (B1)	0.054700
30	RIBOFLAVIN (B2)	0.054700
	MINERAL, CHROMIC ACETATE, (MONOHYDRATE) KOSHER	0.015480
	FOLIC ACID - PURE	0.015333
	MINERAL, SODIUM MOLYBDATE,	0.005160



	(DIHYDRATE) (ACS REAGENT GRADE), KOSHER	
	MINERAL, SODIUM SELENITE, (ANHYDROUS) KOSHER	0.004154
5	Total	100.000000

Canola oil is from Columbus Foods, US

MCT oil is from Stepan Company

EPAX® 4510 (Marine oil) is from Pronova Biocare, Lysake, Norway

10 DHA Gold® (Algae oil) is from Martek, Columbia, Maryland

Ca Caseinate is from New Zealand Milk Products

Benefiber® is from Novartis Nutrition Corporation

Arg, Leu, Val, Met, Phe, are from Ajinomoto, JP

Corn syrup (25DE) is from Cargill

15 as Flavor vanilla flavor is used

Vit/min Premix is from Fortitech

Mono- and diglycerides are from American Ingredients

Antifoam is from Dow Corning

## 20 Example 6

A cancer supplement in form of a ready to drink composition. The composition is prepared according to the method described in Example 5.

		g / 100 ml
Water		72.7655747
Protein	Na-caseinate	5.2320000
	Ca-Caseinate	2.3980000
	L-Leucine	1.3050003
	L-Arginine	0.6199996
	L-Methionine	0.0752100
Fat	Fishoil	2.8002100
	Sunfloweroil	2.0100003
	MCT oil	0.5003100
	Inulin	1.1172500
Carbohydrate	Sucrose	1.0900000
	Maltodextrin	16.5445530
	Fructose	0.5450000
	Partially hydrol. Guar Gum	0.5253800
	Vitamin E (alpha- tocopherol)	0.0763000
Vitamins/Minerals		0.2235515
Flavor		0.7517000
Stabilizer		0.0893778
Sweetener		0.0654000
K2H-citrate		0.1962000
K-citrate		0.0599500

Equivalent compositions may be obtained employing 0.0327 g Vitamin E per 100 ml.

The examples illustrate compositions useful for example to provide sources of amino acids to counteract protein-energy malnutrition, to optimize protein synthesis and muscle building capacity, help restore and maintain muscle mass and weight, support a potentially improved response to cancer treatment and improve quality of life, on administration of for example

5 from 1 to 6 servings of 200 ml per day.

Claims

1. A composition comprising leucine and at least one of isoleucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, or histidine in free and/or salt form, wherein  
5 leucine in free and/or salt form is present in an amount of at least about 10 to about 35% by weight based on the weight of total amino acids.
2. A composition comprising leucine and at least one of isoleucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, or histidine in free and/or salt form, wherein  
10 total leucine is present in an amount of at least about 20 to about 35% by weight based on the weight of total amino acids.
3. A composition comprising a combination of
  - a) essential and, optionally, conditionally essential amino acids in free form and/or salt  
15 form, and
  - b) intact protein, wherein  
total essential and, optionally, conditionally essential amino acids are present in an amount of about 55 to about 75% by weight based on the weight of total amino acids.
- 20 4. A composition of claim 3 wherein a) comprises leucine and at least one of isoleucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, or histidine in free and/or salt form.
5. A composition of claim 4 wherein total leucine is present in an amount of about 20 to  
25 about 35% by weight based on the weight of total amino acids.
6. A composition according to any preceding claim further comprising arginine in free and/or salt form in an amount of at least about 5 to about 40% by weight and/or methionine in free and/or salt form in an amount of at least about 0.5 to about 5% by weight based on  
30 the weight of total amino acids.
7. A composition according to any preceding claim further comprising n-3 polyunsaturated fatty acids.

8. A composition according to claim 7 wherein n-3 polyunsaturated fatty acids are chosen from at least one of alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid.
9. A composition according to claim 8 comprising at least about 1 g EPA per serving or at least about 2 g EPA per daily dose.
10. A composition according to any preceding claim further comprising tocopherol and/or tocotrienol.
11. A composition according to claim 10 comprising at least about 50 mg vitamin E (alpha-tocopherol) per serving or at least about 150 mg vitamin E per daily dose.
12. A composition according to any preceding claim comprising from about 6 g to about 18 g amino acids in free and/or salt form per daily dose.
13. A composition according to any preceding claim comprising from about 5 to about 10 g leucine in free and/or salt form per daily dose.
14. A composition according to any preceding claim comprising from about 6 to about 21 g total essential and/or conditionally essential amino acids per serving.
15. A pharmaceutical or nutritional composition or dietary supplement comprising a composition according to any one of claims 1 to 14 and a pharmaceutically or nutritionally acceptable carrier.
16. A kit comprising a composition according to any preceding claim for separate, sequential or simultaneous administration in conjunction with one or more anti-cancer drug(s).
17. A composition or kit according to any preceding claim for use as a medicament.
18. A composition according to any one of claims 1 to 15 for controlling tumor-induced weight loss, such as cachexia, and/or anorexia, for stimulating muscle protein synthesis or ameliorating loss of muscle in a human, or for the dietary management of malnutrition.

19. A method for controlling tumor-induced weight loss, such as cachexia, and/or anorexia, for stimulating muscle protein synthesis or ameliorating loss of muscle in a human, or for the dietary management of malnutrition, comprising enterally administering to a human in need of such treatment a composition according to any one of claims 1 to 15.
20. A use of a composition according to any one of claims 1 to 15 in the manufacture of a medicament for controlling tumor-induced weight loss, such as cachexia, and/or anorexia, for stimulating muscle protein synthesis, or ameliorating loss of muscle in a human, or for the dietary management of malnutrition.

Figure 1

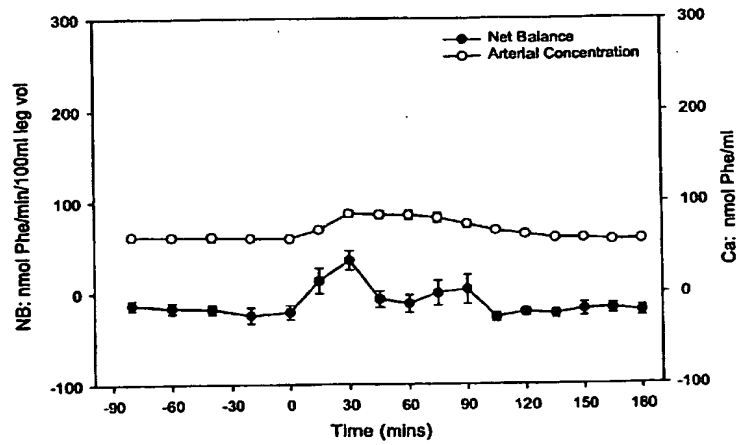


Figure 2

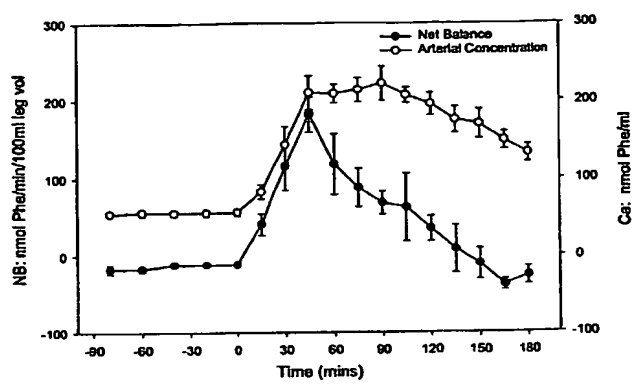
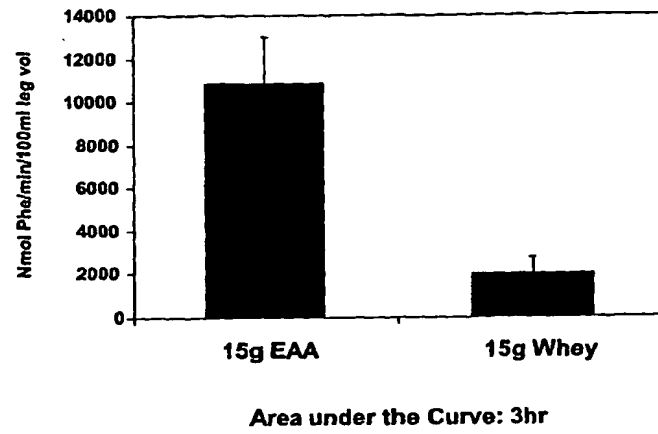


Figure 3





# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/10482

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61P35/00 A23L1/29

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 817 695 A (PELLICO MICHAEL A) 6 October 1998 (1998-10-06) the whole document	1-20
X	US 6 420 342 B1 (HAGEMAN ROBERT JOHAN JOSEPH ET AL) 16 July 2002 (2002-07-16) column 6, line 59 -column 7, line 2 column 9, line 33-48 column 11, line 62-67 examples 1,2	1-20
X	US 6 245 379 B1 (LEPINE ALLAN J) 12 June 2001 (2001-06-12) column 1, line 16 -column 2, line 38 column 3, line 57 -column 5, line 47	1-20
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

18 February 2004

Date of mailing of the international search report

27/02/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Paul Soto, R

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/10482

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 576 351 A (BARBUL ADRIAN ET AL) 19 November 1996 (1996-11-19) column 3, line 6-21 column 4, line 45 -column 5, line 6; tables ---	1-6, 10-20
X	"WPI WORLD PATENT INF" WPI WORLD PATENT INF, XP002099910 the whole document & JP 01 301619 A 5 December 1989 (1989-12-05) ---	1,2,6, 12-20
A	US 6 387 883 B1 (COPE FREDERICK OLIVER ET AL) 14 May 2002 (2002-05-14) the whole document ---	1-20
A	VENTRUCCI G ET AL: "Effect of a leucine-supplemented diet on body composition changes in pregnant rats bearing Walker 256 tumor" BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, vol. 34, no. 3, March 2001 (2001-03), pages 333-338, XP009026255 ISSN: 0100-879X the whole document -----	1-20

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/10482

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19 (industrial applicability)  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210**

Continuation of Box I.1

Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

---

Continuation of Box I.1

Claims Nos.: 19 (industrial applicability)

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/10482

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 5817695	A	06-10-1998	CA	2244608 A1	24-06-1999
			EP	0925726 A1	30-06-1999
US 6420342	B1	16-07-2002	AU	5685601 A	20-11-2001
			CN	1429113 T	09-07-2003
			EP	1282426 A1	12-02-2003
			JP	2003532679 T	05-11-2003
			WO	0185178 A1	15-11-2001
			US	2002183263 A1	05-12-2002
US 6245379	B1	12-06-2001	US	2002018828 A1	14-02-2002
			AU	753725 B2	24-10-2002
			AU	6028399 A	17-04-2000
			CA	2346423 A1	06-04-2000
			EP	1130974 A1	12-09-2001
			JP	2002525087 T	13-08-2002
			NZ	509776 A	25-07-2003
			WO	0018247 A1	06-04-2000
US 5576351	A	19-11-1996	AT	192037 T	15-05-2000
			AU	7148791 A	24-07-1991
			CA	2071971 A1	30-06-1991
			DE	69033521 D1	31-05-2000
			DE	69033521 T2	31-08-2000
			EP	0507872 A1	14-10-1992
			ES	2146199 T3	01-08-2000
			JP	5502881 T	20-05-1993
			JP	3287842 B2	04-06-2002
			WO	9109524 A1	11-07-1991
US 6387883	B1	14-05-2002	US	6326355 B1	04-12-2001
			US	6077828 A	20-06-2000
			US	2002099020 A1	25-07-2002
			AT	254454 T	15-12-2003
			AU	716532 B2	24-02-2000
			AU	2742497 A	12-11-1997
			CA	2252513 A1	30-10-1997
			CA	2355247 A1	30-10-1997
			DE	69726280 D1	24-12-2003
			EP	0914111 A2	12-05-1999
			JP	11508282 T	21-07-1999
			NZ	332291 A	28-07-2000
			NZ	504416 A	25-05-2001
			WO	9739749 A2	30-10-1997